REMARKS

Claims 22 and 24-57, as amended, as well as new claim 98, are currently pending in the above-captioned application. Claims 23 and 39 have been cancelled without prejudice. The subject matter of claim 39 has been incorporated into independent claim 22. Claims 40 and 45 have been amended to correct dependencies due to the cancellation of claim 39. Claim 44 has been amended to capitalize each letter of " genePORTER" and "Transfast." Claim 47 has been amended to be written in independent form. Claim 48 has been amended to more clearly recite that the protein undergoes controlled release from the microspheres (*see, e.g.*, Specification, page 28, lines 1-20). Claim 55 has been amended to clarify units, *i.e.*, that at least 100 microns of protein is loaded per 10 mm of conduit (*see, e.g.*, Specification, page 7, line 21). Claim 57 has been amended to be written in independent form. New claim 98 recites the subject matter of previously presented claim 38.

In addition, in response to the Examiner's request at page 2 of the Office Action, Applicants have also amended the specification to capitalize each letter of "genePORTER" and "Transfast." Applicants note, however, that Applicants have already identified these trademarked terms with respect to their generic terminology, *e.g.*, at pages 13-14 of the originally filed specification. No new matter has been added by the amendments to the instant specification and/or claims.

Initially, Applicants note the Examiner's statement that claim 22 was numbered incorrectly by Applicants and should have been grouped in Group I and, since Group II was elected, that claim 22 should be removed from consideration. Applicants note that neither claim was numbered incorrectly by Applicants. Applicants further respectfully submit that the claim which should be removed from consideration is claim 23, which depends from cancelled claim 1, and not claim 22. As such, Applicants have cancelled, without prejudice, claim 23, which Applicants submit belongs in non-elected Group II.

THE REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

On pages 2-3 of the Office Action, claims 38 and 55 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable one skilled in the art to make and/or use the invention. Applicants respectfully traverse this rejection for the following reasons.

Regarding claim 38, the Office Action states that the microporosity of the outer surface of the wall is not disclosed relative to the luminal surface of the conduit.

Applicants respectfully submit that support for differential or asymmetrical microporosity between the outer and luminal wall surfaces, as recited in claim 38, can be found in the originally filed specification, *e.g.*, at page 29, lines 12-18, and at page 31, line 34 through page 32, line 5. Furthermore, this feature was recited in originally filed claim 38. Accordingly, this feature is supported by the originally filed specification.

Regarding claim 55, the Office Action states that 100 mm of protein cannot be loaded into 10 microns of conduit. Applicants appreciate the Examiner's recognition of this typographical error. As a result, Applicants have amended claim 55, as suggested by the Examiner, to recite that at least 100 microns of protein is loaded per 10 mm of conduit.

Claim 48 was rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim subject matter of the invention. The Examiner alleged that the term "progressively" was indefinite. Although Applicants do not agree that the term "progressively" is indefinite, in order to expedite prosecution, Applicants have amended claim 48 to recite that "the microspheres contain a protein that undergoes controlled release from the microspheres." Such language is well known in the art and is supported in the originally filed specification, *e.g.*, at page 28, lines 1-20.

For the foregoing reasons, Applicants respectfully request that the rejections of claims 38, 48, and 55 be reconsidered and withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 102(E) SHOULD BE WITHDRAWN

On pages 3-4 of the Office Action, claims 22, 24-27, 47-49, and 51 were rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by published U.S. Patent Publication No. 2002/0155092 to Leong *et al.* (" the '092 publication"). Applicant respectfully traverses this rejection for the following reasons.

The '092 publication teaches biodegradable polymers comprising repeat units derived from cyclic phosphate monomers and optionally further comprising repeat units derived from lactide or caprolactone monomers (*see* the '092 publication, Abstract). The '092 publication also teaches that said biodegradable polymers can be made into articles and microspheres (*see id.*). The '092 publication further teaches methods for the controlled release of a biologically active substance using said biodegradable polymers (*see id.*).

Anticipation requires that each and every feature of a claim be taught by a single prior art reference. However, the '092 publication does not contain all the elements of the instant claims, as amended.

Claim 22, as amended, recites that the nerve guide conduit comprises a gene delivery system. This subject matter was previously presented in claim 39, which Applicants note was not included in the aforementioned rejection. Indeed, Applicants respectfully submit that the '092 publication does not disclose or suggest a gene delivery system in combination with poly(phosphoester) (co)polymers in a nerve guide conduit. Applicants therefore respectfully submit that, by incorporating of the subject matter of claim 39 into claim 22, the amended claim is not anticipated under 35 U.S.C. § 102(e) by the '092 publication.

In addition, Applicants respectfully submit that claim 47 is novel and distinguishable over the '092 publication. Despite the Examiner's indications to the contrary on page 4 of the Office Action, the '092 publication does not disclose or suggest the particular combination of poly(phosphoester) (co)polymer nerve guide conduit with a sustained protein delivery system contained therein, as recited in amended claim 47. While the '092 publication does disclose using its poly(phosphoester) (co)polymers for controlled release of a generic biologically active substance, there is no disclosure or suggestion to combine such a controlled release method with a nerve guide conduit. Applicants therefore respectfully submit that at least claims 48-56 are also not anticipated under 35 U.S.C. § 102(e) by the '092 publication.

Furthermore, Applicants respectfully submit that at least claim 48 and the claims depending therefrom are novel and distinguishable over the '092 publication. Despite the Examiner's indications to the contrary on page 4 of the Office Action, the '092 publication does not disclose or suggest the particular combination of microspheres loaded within a nerve guide conduit, much less the combination of a protein contained in the microspheres, as recited in amended claim 48. Applicants therefore respectfully submit that at least claims 48-56 are also not anticipated under 35 U.S.C. § 102(e) by the '092 publication.

Regarding the Examiner's assertions concerning claim 51, that the nerve guide can alternatively be made from a poly(lactic acid-co-glycolic acid) copolymer, Applicants respectfully submit that claim 51 recites that the *microspheres* in the conduit comprise a PLG/PLGA copolymer, while independent claim 47, from which claim 51 depends, recites that the conduit comprises a poly(phosphoester). Applicants can find no mention in the '092 publication of either microspheres or a nerve guide conduit formed from a poly(lactic acid-co-glycolic acid) copolymer, as asserted in the Office Action. As a result, Applicants respectfully submit that claim 51 is further not anticipated under 35 U.S.C. § 102(e) by the '092 publication.

Additionally, Applicants respectfully submit that new claim 98 is novel and distinguishable over the '092 publication. Indeed, the '092 publication does not disclose or suggest that the outer surface of the conduit's wall has greater microporosity than the conduit's luminal surface, as recited in new claim 98. Because the '092 publication does not disclose or suggest microporosity at all, much less differential microporosity between the outer and inner luminal surfaces of the conduit, Applicants respectfully submit that new claim 98 is not anticipated under 35 U.S.C. § 102(e) by the '092 publication.

For the foregoing reasons, Applicants respectfully request that the rejection of claims 22, 24-27, 47-49, and 51 under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(A) SHOULD BE WITHDRAWN

On pages 4-7 of the Office Action, claims 27-38 were rejected under 35 U.S.C. § 103(a) as being allegedly obvious over the '092 publication in view of U.S. Patent No. 5,026,381 to Li ("Li"). Applicant respectfully traverses this rejection for the following reasons.

Li discloses a hollow conduit for nerve regeneration whose walls are comprised of Type I collagen, as well as methods for its manufacture and for nerve regeneration using same (*see* Li, Abstract and Title). Li also discloses some specific conduit dimensions, *i.e.*, 1mm wide x 5cm long, and having an overall wall thickness of about 0.3mm (*see* Li, column 10, lines 65-68).

Dependent claims 27-38 each incorporate all the features of the claims from which they depend, and claim 22 is the common independent claim for each of them. As discussed above, Claim 22, as amended, recites a nerve guide conduit comprising a gene delivery system. This feature, previously presented in claim 39, was not included in the aforementioned rejection. Accordingly, Applicants respectfully submit that the '092 publication does not disclose or suggest a gene delivery system in combination with poly(phosphoester) (co)polymers in a nerve guide conduit.

Applicants respectfully submit that Li does not remedy the deficiencies of the '092 publication. Li, too, does not disclose or suggest a gene delivery system, as recited in amended claim 22. As dependent claims 27-38 each include all the elements of the claims from which they depend (*i.e.*, claim 22 being the common independent claim for all of them), Applicants respectfully submit that claims depending from amended claim 22 also cannot be obvious over the combination of the '092 publication and Li.

Furthermore, the Examiner notes that the '092 publication does not disclose the porosity of the nerve guide conduit material (claims 27-29). Indeed, Li does not

disclose or suggest a porosity for its nerve guide conduit material either. Applicants, however, respectfully disagree with the Examiner's contention that adjusting the surface porosity to 8% or 35%, as recited in claims 28 and 29, respectively, or even to the range between 2% and 58%, as recited in claim 27, would have been obvious to one of ordinary skill in the art. The Examiner has provided no basis in the prior art for adjusting the surface porosity, especially not to the preferred values of 8% or of 35%, as recited in claims 28 and 29, respectively. There is no disclosure or suggestion in the '092 publication that varying porosity can also affect or control "the extent of permeability (molecular weight cut-off) and rate of permeation," as well as "the susceptibility of the polymeric material towards *in vivo* swelling," as disclosed in the instant specification (*see* Specification at page 21, lines 11-15, emphasis in original), which are important properties that need to be considered when manufacturing a nerve guide conduit.

The Examiner also notes that the '092 publication does not disclose that the outer surface of the wall has greater microporosity than the luminal surface of the conduit (claim 38, as well as new claim 98). Further, Applicants submit that Li does not disclose or suggest a differential microporosity between the outer wall and luminal surfaces either. Indeed, differential microporosity is an important feature of the invention. Applicants respectfully direct the Examiner to pages 31-32 of the specification, which recites:

> It is believed that the luminal layer acts as a semi-permeable membrane that mainly confers molecular mass selectively to the conduit wall, whereas the porous outer wall region controls the rate of permeation and acts as a backing support. This contrasts with the typical asymmetrical membrane where the perm-selective layer is usually the outer skin layer.

Such a conduit construct, *e.g.*, can advantageously "support [nerve] regeneration by allowing inward passage of nutrients and growth or trophic factors from the external host environment, while preventing the inward migration of scar-forming cells" (*See Id.* at page 17, lines 3-5). There is absolutely no disclosure or suggestion in the '092 publication or Li of a nerve guide conduit with differentiated microporosity, as recited in claims 38 and 98, or the unexpected advantages of such a feature. Accordingly, Applicants respectfully submit that the differential microporosity between the outer wall and luminal surfaces recited in claim 38 (and new claim 98) is not obvious over the '092 publication, Li, or the combination thereof. For any of the foregoing reasons, Applicants respectfully request that the rejection of claims 27-38 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

On pages 7-10 of the Office Action, claims 39-40, 42-44, 46, 50, 52-53, and 55-57 were rejected under 35 U.S.C. § 103(a) as being allegedly obvious over the '092

publication in view of published U.S. Application No. 2002/0071828 A1 to Peulve *et al.* ("Peulve"), and further in view of published U.S. Application No. 2003/0027779 A1 to Neuman *et al.* ("Neuman"), U.S. Patent No. 6,485,737 to Mao *et al.* (" Mao"), or U.S. Patent No. 5,258,043 to Stone ("Stone"). Applicant respectfully traverses this rejection for the following reasons.

Initially, Applicants note that claim 39 has been cancelled, making its rejection moot. However, as the subject matter of cancelled claim 39 has been incorporated into independent claim 22, Applicants have addressed the rejection of claim 39 as if it were made against amended claim 22.

Peulve teaches a method of stimulating nerve regeneration by inserting a system of expression of a neurotrophic factor into a biocompatible cuff (*see* Peulve Abstract). Peulve also enumerates synthetic materials and biomaterials for use in its cuff, with preferred materials being collagen or silicone (*see id.*, ¶15), with no disclosure or suggestion of using polymeric phosphorus-containing materials of the '092 publication, no less the poly(phosphoester) (co)polymers recited in the instant claims.

Neuman teaches a method for inducing DNA synthesis in differentiated neurons (*see* Neuman Abstract). Neuman also discloses dioleylphosphatidylethanolamine for use with immunoliposomes containing plasmid DNA (*see id.*, ¶¶144, 146). However, the method for inducing DNA synthesis taught by Neuman involves direct injection into the central nervous system (*see id.*, ¶¶30, 33), with no disclosure or suggestion of using such a DNA synthesis method in combination with a nerve guide conduit, no less one comprising the poly(phosphoester) (co)polymers recited in the instant claims.

Mao teaches a biodegradable terephthalate polyester-poly(phosphonate) composition, as well as articles and methods of using same (*see* Mao Abstract).

Stone teaches a method for making a prosthetic invertebral disc to act as a scaffold for regrowth of invertebral disc material (*see* Stone Abstract and Title). Stone also discloses, in its background section, that U.S. Patent No. 4,458,678 teaches seeding a nerve guide with Schwann cells prior to implantation to increase regrowth (*see id.* column 2, lines 20-22).

Regarding claims 22, 40, 42-44, and 46, the Examiner notes on page 7 of the Office Action that the '092 publication does not disclose using a gene delivery system, but that Peulve does so. Applicants respectfully submit that, while Peulve does disclose a nerve conduit with a gene delivery system, it would not have been obvious for one of ordinary skill in the art to have combined the disclosure of poly(phosphoester) (co)polymers of the

'092 publication with the disclosure of Peulve to attain the nerve guide conduit of amended claim 22.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988). The suggestion of the claimed invention must be in the prior art, not in the disclosure of the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). Moreover, the mere identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. Rather to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). This showing of combinability must be "clear and particular." *In re Dembiczak*, 175 F.3d 994, 999; 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

The Federal Circuit has stated that in determining whether a claim is obvious requires the oft-difficult but critical step of casting the mind back to the time the invention was filed to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one to fall victim to the insidious effect of hindsight reconstruction wherein that which only the inventor taught is used against its teacher. *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). Such hindsight reconstruction does not meet the legal standard for obviousness. It is error to reconstruct the claimed invention from the prior art by using the claims as a blueprint. "When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir 1985). Otherwise, simply combining prior art references without evidence of the required suggestion, teaching or motivation simply takes

the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability, which is the essence of hindsight. *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

The Federal Circuit has stated that the best defense against a hindsight-based obviousness analysis is rigorous application for the requirement for a showing of the teaching or motivation to combine the prior art references. *In re Dembiczak*, 175 F.3d 994, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). In the instant application, Applicants submit that the Examiner has not provided the required suggestion, teaching, or motivation to combine the teachings of the '092 publication with the teachings of Li, Peulve, Neuman, Mao, and/or Stone, which must come from the cited prior art references themselves.

Regarding claims 50, 52-53, and 55-57, Applicants respectfully submit that this rejection is improper, as these claims do not depend from independent claim 22 (that includes the feature of a gene delivery system), but from independent claim 47, which does not contain a gene delivery system, but which contains instead the feature of a sustained protein delivery system. Peulve, Mao, Neuman, or Stone, individually or in combination, do not suggest a sustained protein delivery system. As before, Applicants submit that the Examiner has not provided the required suggestion, teaching, or motivation to combine the teachings of the '092 publication with the teachings of Li, Peulve, Neuman, Mao, and/or Stone, which must come from the cited prior art references themselves.

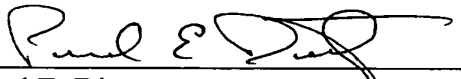
For any one or more of the foregoing reasons, Applicants respectfully request that the rejection of claims 39-40, 42-44, 46, 50, 52-53, and 55-57 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Applicant respectfully submits that the entire application is now in condition for allowance, early notice of which would be greatly appreciated. Should the Examiner disagree, Applicant requests that the Examiner contact the undersigned for a telephonic or in-person interview to resolve any remaining issues regarding the prosecution of the above-captioned application.

No fee is believed to be due for this submission, as this submission does not present more than 4 independent claims nor more than 136 total claims, for which Applicants have already provided payment upon filing. Should any fees be required, however, please charge the required fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date: December 15, 2003



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